REMARKS

These remarks are in response to the Office Action mailed November 8, 2001. Claims 1 to 12 are pending. Claim 11 stands withdrawn as being directed to a non-elected invention. By the present amendment, new claims 13 to 29 have been added. Accordingly, upon entry of the amendment, claims 1 to 10 and 12 to 29 are under consideration.

Regarding the IDS

The Examiner indicates that the IDS filed September 25, 2000, allegedly does not meet the requirements set forth under 37 C.F.R. 1.98 for not listing the title of each journal citation. Submitted herewith is a corrected form PTO 1449 listing the title of each of the journal citations. Applicants respectfully request that the Examiner indicate that each reference has been considered by initialing the corresponding box and returning a copy to the undersigned.

Regarding the Claim Amendments

The amendments to claims are supported throughout the specification or were made to address informalities. In particular, the amendment to claim 1 to recite "to a protein delivered by way of gene therapy" merely clarifies that claim 1 is directed to preventing formation of inhibitory antibodies against the protein encoded by the gene delivered by gene therapy and, therefore, addresses an informality. This amendment to claim 1 is also supported in the specification, for example, at page 7, lines 1-3 and page 8, lines 23-25. The amendment to claim 1 to recite "said gene encoding the delivered protein being the same species as said mammal" indicates that the species of the gene and the species of mammalian recipient of the gene therapy are identical, e.g., mouse gene for mouse recipient, human gene for human recipient, etc. This amendment to claim 1 is supported, for example, at page 13, lines 13-15, which discloses that mice (the recipient) were injected with a vector encoding murine F.IX (Factor IX). The amendment to claim 2 to recite that the mammal "and gene are" both human is also supported, for example, at page 13, lines 13-15. The amendment to claim 3 to recite that the nucleic acid encodes "Factor IX" was made to more clearly indicate the protein encoded by the nucleic acid. The amendment to claim 3 to recite that Factor IX, when expressed in said mammal serves to "produce a beneficial effect" is supported, for example, at page 8, lines 16-17. The

amendment to claim 4 to depend from claim 1 was necessitated by the amendment to claim 3 reciting that the encoded protein is Factor IX and, therefore, addresses an informality. The amendment to claim 6 to recite "mammal" instead of "human" was made to provide adequate antecedent basis for the term "mammal" and, therefore, addresses an informality. The amendment to claim 9 to recite "method of" was made to add missing language to the claim and, therefore, addresses an informality. Thus, as the claim amendments are supported by the specification or were made to address informalities, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

New claims 13 to 29 are supported by the specification. In particular, new claims 13 to 23 substantially parallel originally filed claims 1 to 10 and 12 and are therefore supported by originally filed claims 1 to 10 and 12. New claims 13 to 23 also parallel the amendments to claims 1 to 6 and are therefore supported by the specification as set forth above. Support for claims 13 to 23, 25, 27 and 29, directed to methods of "reducing formation of an inhibitory antibody," can be found in the specification, for example, at page 8, lines 23-25 and at page 8, line 26, to page 9, line 2. Support for claims 24 and 25, which recites that the "mammal has no detectable expression of said gene" can be found in the specification, for example, at page 12, line 28 to page 13, line 10. Support for claims 26 to 29, which recites that the immunosuppressive agent is "administered prior to, concomitantly with or following" or "concomitantly with" said gene therapy can be found in the specification, for example, at page 9, lines 20-22. Thus, as new claims 13 to 29 are supported by the specification new matter has been added and entry thereof is respectfully requested.

I. REJECTIONS UNDER 35 U.S.C. §112

The rejection of claims 1 to 10 and 12 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. The Examiner indicates that the specification enables "A method of inhibiting the formation of inhibitory antibodies in a mammal undergoing gene therapy, said method comprising administering to said mammal an immunosuppressive agent in conjunction with gene therapy; 2) The method of 1, wherein said gene therapy is performed by administering either an adeno-associated virus vector (AAV) or an adenovirus

vector to said mammal, wherein said vector comprises a nucleic acid encoding allogenic Factor IX; wherein said immunosuppressive agent is cyclophosphamide." However, allegedly "the specification does not reasonably provide enablement for the rest of the disclosure." The grounds for this assertion relate primarily to alleged difficulties in achieving a therapeutic benefit via gene therapy, specifically, that "further development in gene delivery vectors and gene expression systems will be required," citing Rubanyi at page 4 of the Office Action; "type of vector and amount of DNA....time course...sites of administration, and successful uptake of the DNA, the level of RNA produced, the stability of the mRNA product, the amount of stability of the protein produced," the "amount of the expressed proteins considered to be therapeutically effective....the specific vector used....animal being treated....disease being treated....poor delivery systems....poor gene expression after genes are delivered...how vectors should be constructed....regulatory sequences," citing Anderson *et al.* at page 5 of the Office Action; and addressing High *et al.* which use an AAV vector for treatment of hemophilia but allegedly "levels of expression of FIX from these vectors are reported to be too low to be of therapeutic value," at page 6 of the Office Action.

In sum, these grounds for rejection exclusively relate to alleged difficulties of gene therapy achieving a therapeutic effect *in vivo*. However, Applicants first point out that many of the alleged difficulties with gene therapy have been resolved. In fact, Applicants could submit numerous issued patents and peer review scientific publications containing data supporting this position.

However, Applicants need not submit supporting documentation because, quite simply, aside from claims 3 and 15 Applicants claims do not require achieving therapeutic gene therapy. Rather, the claims are directed to preventing or reducing formation of an inhibitory antibody (antibodies) to a protein that is delivered to a mammal by way of gene therapy. Thus, aside from claims 3 and 15 the claimed methods do not require achieving a therapeutic benefit, rather, only that production of an inhibitory antibody (antibodies) to a protein delivered to a mammal via gene therapy be reduced or prevented. Accordingly, as claims 1, 2, 4 to 10 and 12, and new claims 13, 14 and 16 to 29 do not require that gene therapy achieve a therapeutic benefit, Applicants need not enable therapeutic gene therapy. Applicants therefore need not address any of the grounds for rejection relating to the alleged difficulties associated with therapeutic gene therapy in order to enable claims 1, 2, 4 to 10 and 12, and new claims 13, 14 and 16 to 29.

The Examiner also indicates that allegedly "the specification and the state of the art fail to provide sufficient guidance for one skilled in the art to use the method for preventing the formation of inhibitory antibodies in any mammal undergoing gene therapy." Potter *et al.*, a review that describes studies using various immunosuppressive agents to prevent neutralizing antibody formation in which the results were varied, is cited as allegedly supporting this position by (see page 7 of the Office Action).

The specification adequately enables the claims, as originally filed and as presently amended. First of all, the claims are directed to preventing or reducing formation of an inhibitory antibody or antibodies to a protein delivered to a mammal by way of gene therapy, said method comprising administering to said mammal an immunosuppressive agent in conjunction with said gene therapy, said gene encoding the delivered protein being the same species as said mammal. Thus, as the claims require preventing or reducing formation of an inhibitory antibody, if an immunosuppressive agent does not prevent or reduce formation of an inhibitory antibody in a particular context than the immunosuppressive agent is not encompassed within the claims. Accordingly, that some immunosuppressive agents may not reduce or prevent formation of an inhibitory antibody or antibodies, as discussed in Potter *et al.*, is irrelevant to enablement of Applicant's claims since such immunosuppressive agents would not be included in the claims.

Furthermore, the specification exemplifies three different immunosuppressive agents that are able to prevent or reduce formation of inhibitory antibodies against a protein delivered by way of gene therapy. For example, mice administered anti-CD-40L with murine Factor IX delivered via gene therapy and mice administered cyclophosphamide with murine Factor IX delivered via gene therapy exhibited partial and nearly complete correction of aPTT times, respectively (see paragraph bridging pages 13 and 14). For both anti-CD-40L and cyclophosphamide immunosuppressive agents, titers of anti-Factor IX antibodies in the mice were either significantly reduced or were undetectable (see table, page 14). In addition, mice administered FK506 in combination with murine Factor IX delivered via gene therapy exhibited shorter aPTT times than mice which were not treated with FK506 (see page 15, lines 23-26 and Figure 5). Thus, the data in the specification exemplifying three different immunosuppressive agents demonstrates that formation of inhibitory antibodies against a protein delivered by way of gene therapy can be reduced or prevented using any of a number of immunosuppressive agents.

As to preventing formation of inhibitory antibodies, the specification discloses that anti-Factor IX antibodies in a mouse administered cyclophosphamide in conjunction with murine Factor IX delivered via gene therapy were undetectable at 1 and 2 months (see table, page 14, "CYP"). Thus, the specification adequately enables preventing formation of inhibitory antibodies as claimed.

Further in support of Applicants position, submitted herewith is Exhibit A (Herzog *et al.*, Molecular Therapy 4:192 (2001)), which describes Factor IX gene transfer in combination with cyclophosphamide immune suppression in a hemophilic dog (null mutation in *F9*). The data in Exhibit A demonstrate that treatment of a dog with a combination of Factor IX gene transfer and cyclophosphamide immune suppression blocked formation of anti-canine Factor IX antibodies and resulted in sustained expression (greater than 8 months) of canine Factor IX levels sufficient for partial correction of coagulation (see abstract). The data further indicate that anti-canine Factor IX antibodies were undetectable 15 weeks after the first injection with canine Factor IX (see Figure 2D, page 194; see, also, Table 2, page 198). Thus, Exhibit A, which describes data demonstrating preventing production of inhibitory antibodies to Factor IX delivered by way of gene therapy using an immunosuppressive agent, corroborates the data in the specification indicating that formation of inhibitory antibodies can be prevented as is claimed.

As to the Office Action indicating that the data disclosed in the specification cannot be extrapolated to any mammal, Exhibit A demonstrates that treatment of a dog with a combination of Factor IX gene transfer and cyclophosphamide blocked formation of anti-canine Factor IX antibodies, and resulted in sustained expression of canine Factor IX levels sufficient for partial correction of coagulation. Thus, Exhibit A also corroborates that formation of inhibitory antibodies in mammals in general can be prevented or reduced as is claimed.

As to claim 3, Applicants disagree that complete correction of a genetic defect is required in order to enable this claim. Again, as discussed above, the claimed methods are directed to preventing or reducing formation of an inhibitory antibody (antibodies) to a protein delivered to a mammal by way of gene therapy. Nevertheless, without acquiescing to the propriety of the rejection and solely in order to further prosecution of the application, claim 3, has been amended to recite that the protein delivered is "Factor IX," which produces a "beneficial effect." Claim 15, which depends from claim 13, parallels claim 3. In view of the specification as corroborated by Exhibit A, each of which demonstrate that Factor IX levels sufficient to produce

a beneficial effect can be attained in a mammal, claims 3 and 15 are adequately enabled. Accordingly, these grounds for rejection should be withdrawn.

In sum, as the grounds for the rejection relating to therapeutic gene therapy are not applicable to claims 1, 2, 4 to 10 and 12, and new claims 13, 14 and 16 to 29, and one skilled in the art could use various immunosuppressive agents to either prevent or reduce formation of an inhibitory antibody (antibodies) to a protein delivered to mammals, in general, by way of gene therapy, and one skilled in the art could practice claims 3 and 15 without undue experimentation, the claims are adequately enabled. Accordingly, the rejection under 35 U.S.C. §112, first paragraph should properly be withdrawn.

The rejection of claims 4 and 6 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is respectfully traversed. The Examiner indicates that the terms "protein" in claim 4 and "human" in claim 6 lack adequate antecedent basis.

Claim 4 has been amended to provide adequate antecedent basis for the term "protein" as set forth above. Claim 6 has been amended to substitute the term "mammal" for the term "human" which, as the Examiner correctly points out, is recited in claim 1. Accordingly, in view of the amendments, claims 4 and 6 are clear and definite. As such, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §102

The rejection of claims 1 to 5, 9, 10 and 12 under 35 U.S.C. §102(b) as allegedly anticipated by Tengborn *et al.* (Haemophilia 4:56 (1998)) is respectfully traversed. The Examiner indicates that Tengborn *et al.* allegedly describe that "a high dose regimen with factor IX in combination with cyclophosphamide and gammaglobulin intravenously according to the Malmo model has been used for the induction of immune tolerance in haemophilia B complicated inhibitor formation with a success rate of 85% (6 out of 7 cases)."

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (*In re Spada*, 15 USPQ 2d 1655 (Fed. Cir. 1990), *In re Bond*, 15 USPQ 2d 1566 (Fed. Cir. 1990).

Claims 1 to 5, 9, 10 and 12, prior to the present amendment and as amended are not anticipated by Tengborn *et al.* New claims 13 to 29 are also not anticipated by Tengborn *et al.* The claims, *inter alia*, require that formation of inhibitory antibodies against the protein delivered by way of gene therapy be prevented. In contrast, Tengborn *et al.* describe "continuous infusion" of "Factor IX" given at "a dose of around 300 units per kg body weight daily for 3 weeks." (see, Tengborn *et al.*, abstract) Tengborn *et al.* therefore fail to teach or suggest administering an immunosuppressive agent in conjunction with gene therapy as claimed. Accordingly, as Tengborn *et al.* fail to disclose each element of the claimed invention as required under 35 U.S.C. §102, and should be withdrawn.

Furthermore, in order for a rejection under 35 U.S.C. §102 to be proper, the cited reference must contain an enabling disclosure. [see M.P.E.P. §§2121.01 and 2121.02] However, Tengborn *et al.* were unsuccessful in inducing immune tolerance using their protocol. For example, the authors state that "The immune tolerance induction was thus not successful in the two cases presented here." (see, Tengborn *et al.*, page 59, the first sentence of the second paragraph). Thus, as Tengborn *et al.* failed to demonstrate induction of immune tolerance they do not enable any immunosuppression method, let alone the claimed methods.

In sum, as Tengborn *et al.* fail to teach or suggest each and every element claimed nor enable any immunosuppression method, this reference cannot anticipate claims 1 to 5, 9, 10 and 12, prior to the present amendment and as currently amended, nor new claims 13 to 29. Accordingly, the rejection under 35 U.S.C. §102(b) over Tengborn *et al.* is improper and Applicants respectfully request that it be withdrawn.

The rejection of claims 1 to 6, 9, 10 and 12 under 35 U.S.C. §102(b) as allegedly anticipated by Trapnell *et al.* (WO 97/39776) is respectfully traversed. The Examiner indicates that Trapnell *et al.* allegedly describe "a method of gene therapy in host, comprising the steps of (a) administering to a host (I) an adenoviral vector including at least one DNA sequence encoding a therapeutic agent; (ii) deoxyspergualin, and (iii) cyclophosphamide."

Claims 1 to 6, 9, 10 and 12, prior to the present amendment and as amended are not anticipated by Trapnell *et al.* New claims 13 to 29 are also not anticipated by Trapnell *et al.*

As discussed above, the claims, *inter alia*, require that formation of inhibitory antibodies against the protein delivered by way of gene therapy be prevented. In contrast, Trapnell *et al.*

describe suppression of an immune response against adenovirus gene delivery vehicle (see, for example, page 1, second paragraph, last sentence, see also, page 7, paragraph 1, last sentence and paragraph 3; page 13, second paragraph; page 16, last paragraph; paragraph bridging pages 35 and 36). Accordingly, Trapnell *et al.* fail to disclose each element of the claimed invention as required under 35 U.S.C. §102. As such, the rejection under 35 U.S.C. §102(b) over Trapnell *et al.* is improper and Applicants respectfully request that it be withdrawn.

The rejection of claims 1 to 10 and 12 under 35 U.S.C. §102(e) as allegedly anticipated by High *et al.* (U.S. Patent No. 6,093,392) in further view of Smith *et al.* (Gene Therapy 3:496 (1996)) is respectfully traversed. The Examiner indicates that High *et al.* claim a method of treating hemophilia in a mammal by administering recombinant AAV encoding factor IX. The Examiner further indicates that High *et al.* teach that "adenoviral vectors are well known in gene therapy and have been used to effect expression of high levels of canine factor IX in immunodeficient/immunocompetent mice when the virus is administered in conjunction with immunosuppressive agent." Smith *et al.* allegedly describe that "multiple intravenous administration of adenovirus vectors resulting transgene expression can be accomplished in immune competent animals treated with a short course of immunosuppression at the time of vector delivery." Smith *et al.* therefore allegedly "demonstrates that employing the immunosuppressive agent cyclophosphamide, in conjunction with a method of gene therapy for treating hemophilia to increase the efficiency of gene transfer and the expression of the nucleic acid encoding the protein Factor IX in a mammal was anticipated by High in view of Smith."

Applicants note that this rejection was made under 35 U.S.C. §102 even though the Examiner has combined two references. In this regard, multiple references are only proper in making a §102 rejection where the extra reference(s), in this case Smith *et al.*, prove the primary reference contains an enabling disclosure, explains the meaning of a term or shows a characteristic not disclosed is inherent. [M.P.E.P. §2131.01] Thus, the primary cited reference, in this case High *et al.*, must still teach each element claimed for a rejection to be proper under 35 U.S.C. §102.

In the present case, each element of claims 1 to 10 and 12, prior to the present amendment and as amended are not described by High *et al.* Nor is each element of new claims 13 to 29 described by High *et al.*

High *et al.*, for example, do not describe that formation of inhibitory antibodies against a protein delivered via gene therapy can be prevented by administering an immunosuppressive agent. Thus, High *et al.* do not describe each element of claims 1 to 10 and 12. Accordingly, High *et al.* cannot anticipate these claims and, therefore, the rejection under 35 U.S.C. §102(e) over High *et al.* is improper.

Furthermore, because High *et al.* do not describe each and every element of claims 1 to 10 and 12 it is improper to combine an additional reference (i.e., Smith *et al.*) with High *et al.* Thus, the rejection under 35 U.S.C. §102(e) over High *et al.* in further view of Smith *et al.* is improper and should be withdrawn.

Nor does Smith *et al.* teach each element of claims 1 to 10 and 12. As with Trapnell *et al.*, Smith *et al.* at most describe transient immunosuppression that "prevented the formation of anti-adenovirus neutralizing antibody" (see abstract; see, also, page 496, "Introduction," second column, first paragraph; and page 499, under "Discussion," second paragraph). However, Smith *et al.* fail to teach or suggest administering an immunosuppressive agent to prevent formation of inhibitory antibodies against a protein delivered via gene therapy as claimed. Thus, Smith *et al.* cannot anticipate claims 1 to 10 and 12.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 10 and 12 to 29 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

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